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(54) Title: COMPOSITIONS FOR THE TREATMENT AND PROPHYLAXIS OF INFLAMMATIONS AND DERMATOSES INDUCED BY VIRUSES AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract

The invention relates to new cosmetic and/or medicinal compositions which beneficially affect virus-induced infections and inflammations of the skin and mucosa and promote the regeneration of the dermatoses caused, i.e. the compositions are able to restore the initial conditions of the skin.

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COMPOSITIONS FOR THE TREATMENT AND PROPHYLAXIS OF INFLAMMATIONS AND DERMATOSES INDUCED BY VIRUSES AND PROCESS FOR THE PREPARATION THEREOF

The invention relates to new cosmetic and/or medicinal compositions which beneficially affect virus-induced infections and inflammations of the skin and mucosa and promote the regeneration of the dermatoses caused, i.e. the compositions are able to restore the initial conditions of the skin.

The compositions of the invention are specially suitable for the treatment of infections and dermatoses induced by herpes virus.

Several patents report on products suitable for the treatment of herpes. The US patent specification No. 317976 recommends the hydrophilic ointment tricontanol. Tricontanol (melissyl alcohol, myricyl alcohol, $CH_3(CH_2)_{28}CH_2OH$) alleviates pain, heals the wounds developing in acne and perioral dermatitis, exerts antiinflammatory action and restores the normal lipid content of the skin. In the Swiss patent specification No. 005810 (CIBA) an oral stick formulation containing heparin and dissociating zinc salt are proposed. The Israeli patent specification No. 065184 (see British patent specification No. 029749 and US patent specification No. 4,700,293, too) recommends a combination of glycyrrhizin and steroids (e. g. triamcinolon) or viricidal agents (e. g. idoxuridine). The first is proposed for the treatment of aphtha with adjuvant stomatitis while the latter one for oral, nasal or genital herpes. The Roumanian patent specification No. 098473 describes a mixture of poplar bud extract, arnica blossom tincture and melilot oil. The Hungarian patent specification No. 001224

reports on antiherpetic 2'-chloro-2'-deoxyuridines substituted in position 5.

The cited patents also confirm that in this field of indication the use of natural substances is becoming popular world-wide, too. The present invention is also a representative of this trend of development, and is based on the observation that active ingredient concentrates can be prepared from particular natural substances by a specific process which can be used, alone or in combination, for the production of cosmetic agents or medicinal cosmetics of improved activity. Their activity can be further increased by applying adjuvants or specific formulations.

The invention relates to compositions of manifold application with viricide, antiinflammatory and regenerating activity wherein the concentrations of the ingredients given % by weight are as follows:

Glycyrrhizin, preferably in the form of sweet-root extract	0.005-0.4
Rosemary acid, preferably in the form of plant extract	0.005-0.4
Thyme oil (thymol content min. 20 %)	0.001-0.5
Allantoin	0-0.5
Polydocanol	0-5.0
α-Bisabolol	0.005-0.5
Soluble collagen	0.001-0.05
Irgasan OP 300	0-0.5
Ethanol	0-90.

The compositions may contain further carriers, additives and auxiliary materials usually applied in the preparation of cosmetic or medicinal compositions, preferably water, propyleneglycol, acrylamide-sodium acrylate copolymer, PEG-7,

glycerol cocoate and isooctyl nonanoate, as well as solubilizing agents, lipids, preservatives and fragrance components in hydrogel, lotion-ointment, liquid emulsion, spray, stick or drop formulation.

As regards the constituents of the composition it is known from literature sources that rosemary acid (caffeoyl-α-hydroxy-dihydrocaffeic acid), together with quinic acid, chlorogenic acid and caffeic acid, is present in plants of the labiate family (Laminaceae), mainly in Melissa officinalis, Hyssopus officinalis, Rosmarinus officinalis and Salvia officinalis. Its virostatic, antibacterial and antimycotic potency is reported by I. K. Heimann and W. Schultze in the Zeitschrift für Phythotherapie Sept. 1988, 82-83.

Because of their sweet taste the sweet root (Glycyrrhiza glabra) extracts are used as sweeteners to improve taste and as expectorants (B. Issekutz: (Drug prescription, Gyógyszerrendelés p. 600 Medicina, Budapest, 1979). The regular use of standard preparations may reduce the increased tension of the stomach wall and the inflammation of gastric mucosa (Gizella Verzár Petri: Gyógynövények a gyógyászatban (Medicinal plants in therapy), p. 92, Medicina, Budapest, 1984). Soviet authors [I. A. Murajev 25 et al.: Farmacia (Moscow), 94 (2), 84, 1979] found it to be more or less equiactive with prednisolone in contact allergy and dermatitis. Glycyrrhizin, the major constituent of sweet root has mineralocorticoid, antiinflammatory, antiedema and epithelizing (wound healing) properties.

The volatile oil of thyme (Thymus vulgaris) contains mainly thymol, carvacrol, p-cymol, furthermore linalool, borneol, geraniol and ß-pinene. Due to its thymol content the thyme oil has viricide effect and inhibits a major part of wound bacteria even at 3000fold dilution (Gizella Verzár

Petri: Medicinal plants in therapy, Medicina, Budapest, 1984, p. 74.).

The α-bisabolol is one of the major components of camomile (Matricaria chamomilla). Primarily it has antiinflammatory effect and promotes granulation.

The allantoin promotes the skin-regeneration and hydration.

The collagens, which can be found in the skin, also play role in hydration, but based on other mechanism.

The polydocanol is ingredient of numerous medicinal and cosmetic composition. It has analgetic and local anaesthetic effect.

According to the literature individual components of the preparation of the present invention are applied, though with varying frequency, in medical practice, but no preparation which has similar composition as that of the invention and is produced with a process similar to the disclosed one. The product(s) are highly potent, have a broad spectrum of activity and promote the rapid and full regeneration of the affected skin areas.

The preparation of individual medicinal plant extracts, used in the preparation, as well as the composition of the compositions are summed up as follows:

Characterization of components:

1.) Dry extract with rosemary acid content:

An aqeous alcohol (methanol, ethanol, isopropanol) extract is prepared from the leaves of a plant from Laminaceae family, e.g. rosemary, melilot (Melissa officinalis), Salvia officinalis and Hyssopus officinalis, etc. After removing the solvent the residue is acidified to pH 2-3 with an inorganic acid, the mixture is extracted with a

water immiscible solvent (ether, chloroform, dichloromethane, ethyl acetate, etc.), the layers are separated and the solvent is removed from the organic layer yielding a dry extract.

2.) Dry extract containing glycyrrhizin:

The sweet root is extracted with water or aqueous alcohol (methanol, ethanol, isopropanol) and the solvent is removed. The aqueous solution is acidified to pH 2-3 with an inorganic acid, the precipitated mixture is filtered, the precipitate is dried, dissolved in ethanol, the pH of the solution is adjusted to 7-8 with ammonia, filtered and evaporated to dryness.

3.) Thyme oil. Aetheroleum thymi (Hungarian Pharmacopoea No. 7.)

Purified volatile oil prepared from the blossoming, fresh branch tops of the garden thyme (Thymus vulgaris) with steam distillation. The product has a phenol content not less than 20.0 % (v/w) expressed in thymol.

The examination of the effect of the compositions:

The product is specifically beneficial for symptoms of the mucosa (oral and genital) induced by herpes simplex virus. Applied in the early stage the development of erythema and edema is suppressed and recovery is accelerated. In recurrent cases, applied before the development of symptoms, superinfection is fully inhibited. Furthermore, subjective symptoms, such as itching and stretching, are alleviated, and recovery is rapid and traceless. The skin becomes refreshed and hydrated.

Two figures are shown to demonstrate the efficacy of the product. Figure 1 presents the results of the comparative study of the preparation of the invention (herpes

gel prepared according to procedure 1) and that of the commercial control products, together with the duration of recovery of untreated cases. The following control preparations were tested in the study (Figure 1 shows the mean values of the results obtained):

1.) Medicinal gel and paint formulation containing the extract of 15 % (w/w) Chelidonium herba, 3 % (w/w) Menthae piperita folium, 1 % (w/w) Calendula officinalis, 2 % (w/w) Thymi herba and 2 % (w/w) Millefolii herba, prepared with 50 % (w/w) ethanol.

2.) Medicinal suspension ointment formulation containing 0.8 % (w/w) of 3-(2-deoxy-D-ribofuranosyl)-5-isopropyluracyl.

3.) Medicinal alcoholic gel formulation containing 0.2 % (w/w) primicium sulfuricum and 2 % (w/w) lidocain.

4.) Painting agent containing 0.5 % (w/w) of zinc sulfate widely used in magistral preparations.

The compositions according to the invention reduced the duration of symptom free recovery by 3-4 days compared to the control products and by 7-9 days compared to the untreated control cases. Figure 2 presents the distribution of major recovery categories in the case of the preparation of the invention. According to the chart in about 30 % of the subjects crusts or blisters failed to develop and symptoms were eliminated within 2 days. In about 60 % of the patients only a thin and flexible crust was formed and wound healing was accelerated. Finally in about 10 % of the cases the rate of recovery, both as regards symptoms and wound healing, was similar to that observed with the control preparations. Further observations confirmed that in the case of herpes simplex infections the

product prolonged the interval elapsing till the recurrence of the disease. The symptom free periods may even increase from one to two weeks to 2 months.

From the tests performed the diagram of the hydrating effect of the gel containing the entire active ingredient combination, taken with a SKIN Resistance Meter, is shown in Figure 3.

Preferred formulations of the preparations according to the invention are listed as follows:

In the major part of indications the most advantageous formulation proved to be the rapidly absorbing and penetrating gel form which is easy to handle. The formulations specified (1-3) are partly usual gels and partly microemulsions [values in the table are expressed in % by weight (w/w)]:

Herpes gel formulations	1	2	3
Acrylic acid/Na acrylate copolymer (Hostacerin PN 73)	2.0	1.5	
POE(45) hydrogenated ricinol acid triglyceride (Cremophor RH 40)	2.0	1.5	
POE(7) glycerol cocoate (Cetiol HE)	2.0	5.0	
Isooctadecyl isononanoate (PCL liquid)	2.0	0.3	
Propyleneglycol	8.0	10.0	12.0
Ethanol	30.0	30.0	16.0
POE(9) lauryl alcohol (Polidokanol)	2.0	1.0	2.0
Polyoxyethylene/polyoxypropylene block polymer (Lutrol FC 127)			19.0
Allantoin	0.1	0.2	
α-Bisabolol	0.1	0.05	0.1
1 w/w % Collagen solution	0.5	1.0	0.5

Triclosan (Irgasan OP 300)	0.1	0.1	
Glycyrrhizin	0.1	0.2	0.15
Rosemary acid	0.1	0.2	0.15
Thyme oil	0.02	0.025	0.02
Distilled water ad	100	100	100

The gels are prepared by dissolving allantoin in the bulk of water, then in some cases (formulations 1-2) also the copolimer, using slow stirring. Polydocanol, and in some cases (formulations 1-2) also Irgasan, are dissolved in part of the alcohol. The remaining volumes of alcohol and water are combined and the formerly solubilized thyme oil is added to the mixture. The phases are stirred at low r. p. m., then the lipid additives are poured to the mixture under stirring in the following order: solution of rosemary acid and glycyrrhizin in propyleneglycol and solution of α-bisabolol and collagen. After the addition stirring is continued for further 5-10 minutes. Ointment is also a formulation of choice, see formulations 4 to 6 [values in the table are expressed in % by weight (w/w)]:

Herpes ointment formulations	4	5	6
Liquid paraffin	18.0	18.0	20.0
Stearin	7.0	8.0	9.0
Polyoxyethylene fatty acid ester	6.0	7.0	8.0
Isooctyl stearate	4.0	3.0	3.0
Propyleneglycol	4.0	7.5	12.0
POE-9 lauryl alcohol (polydocanol)		1.0	2.0
Allantoin	0.1	0.1	0.2
α-Bisabolol	0.1	0.15	0.05

1 w/w % Collagen solution	0.5	0.5	1.0
Triclosan (Irgasan DP 300)		0.1	0.1
Glycyrrhizin	0.05	0.1	0.2
Rosemary acid	0.05	0.1	0.2
Thyme oil	0.03	0.04	0.05
Distilled water ad	100	100	100

Ointments are prepared by melting the lipid components and the emulsifier - liquid paraffin, stearin, isooctyl stearate or polyoxyethylene (POE) fatty acid ester, resp. - and heating the mixture to about 70°C. Thereafter the polydocanol is added, and, if desired (formulations 5 and 6), Irgasan. Allantoin is dissolved in water then the aqueous phase is heated to about 70°C.

After completed homogenization, under steady cooling and moderate stirring, at about 60°C the solutions of rosemary acid and glycyrrhizin in propyleneglycol, solutions of α-bisabolol and collagen, then at temperatures lower than 50°C thyme oil are added. Stirring is continued till the mixture becomes cool (about 30°C).

Alcoholic paint, drop or spray are also formulations of choice. The composition of formulations 7 to 9 are listed in the following.

Herpes formulations	7	8	9
Ethanol	20.0	30.0	
Propylene glycol	5.0	8.0	40.0
POE(45) hydrogenated ricinol acid triglyceride (Cremophor RH 40)	1.0	2.0	3.0
Triclosan (Irgasan OP 300)	0.05	0.1	
Allantoin	0.05	0.1	0.2
α-Bisabolol	0.05	0.2	0.1
1 w/w % Collagen solution	1.0	0.5	0.5

Glycyrrhizin		0.05	0.1	0.2
Rosemary acid		0.05	0.1	0.2
Thyme oil		0.02	0.05	0.05
Distilled water	ad	100	100	100

The solutions are prepared by solubilizing first the thyme oil, preferably with POE(45) hydrogenated ricinol acid triglyceride. Irgasan is dissolved in alcohol, and allantoin in the bulk of water. The phases prepared in this way are mixed, then, under constant stirring the solution of α-bisabolol and collagen (formulations 7 and 8) is added to the system, finally the propyleneglycol solution of glycyrrhizin and rosemary acid. Stirring is continued for a couple of minutes after the addition.

Alcoholic painting composition and aerosol foam or spray composition using an appropriate carrier gas can be also prepared.

What we claim is

1. Compositions for the treatment and prophylaxis of inflammations and dermatoses of the skin induced by viruses characterized in that containing ingredients given in % by weight as follows:

Glycyrrhizin	0.005-0.4
Rosemary acid	0.005-0.4
Thyme oil (thymol content min. 20 %)	0.001-0.5
Allantoin	0-0.5
Polydocanol	0-5.0
α-Bisabolol	0.005-0.5
Soluble collagen	0.001-0.05
Irgasan OP 300	0-0.5
Ethanol	0-90

furthermore auxiliary materials usually applied in the preparation of cosmetic and medicinal compositions.

2. Compositions as claimed in claim 1 characterized in that containing as auxiliary materials water, propyleneglycol, acrylamide/sodium acrylate copolymer, PEG-7-glyceryl cocoate, isooctyl nonanoate, solubilizing agents, lipids and preservatives.

3. Compositions as claimed in either of claims 1 or 2 for the treatment and prophylaxis of viral infections and inflammations characterized in that the composition is formulated as a liquid, drop, aerosol, foam, ointment, emulsion or gel formulation.

4. A process for preparing compositions suitable for the treatment and prophylaxis of inflammations and dermatoses of the skin induced by viruses which comprises mixing the ingredients given in % by weight as follows:

Glycyrrhizin	0.005-0.4
Rosemary acid	0.005-0.4
Thyme oil (thymol content min. 20 %)	0.001-0.5
Allantoin	0-0.5
Polydocanol	0-5.0
α-Bisabolol	0.005-0.5
Soluble collagen	0.001-0.05
Irgasan OP 300	0-0.5
Ethanol	0-90

furthermore auxiliary materials usually applied in the preparation of cosmetic and medicinal composition and converting them to cosmetic or medicinal compositions.

5. A process as claimed in claim 4 which comprises using water, propyleneglycol, acrylamide sodium acrylate copolymer, PEG-7-glyceryl cocoate, isooctyl nonanoate furthermore solubilizing agents, lipids and preservatives as auxiliary materials.

6. A process as claimed in either of the claims 4 or 5 which comprises converting the compositions to liquid, drop, aerosol, foam, ointment, emulsion or gel formulations.

7. Therapeutic process for the treatment and prophylaxis of infections, inflammations and dermatoses of the skin and mucosa induced by viruses which comprises treating the infected body surface or the surface susceptible to infection with an effective dose of the preparation containing ingredients given in % by weight as follows:

Glycyrrhizin	0.005-0.4
Rosemary acid	0.005-0.4
Thyme oil (thymol content min. 20 %)	0.001-0.5
Allantoin	0-0.5
Polydocanol	0-5.0
α-Bisabolol	0.005-0.5

Soluble collagen	0.001-0.05
Irgasan OP 300	0-0.5
Ethanol	0-90

furthermore auxiliary materials usually applied in the preparation of cosmetic and medicinal composition.

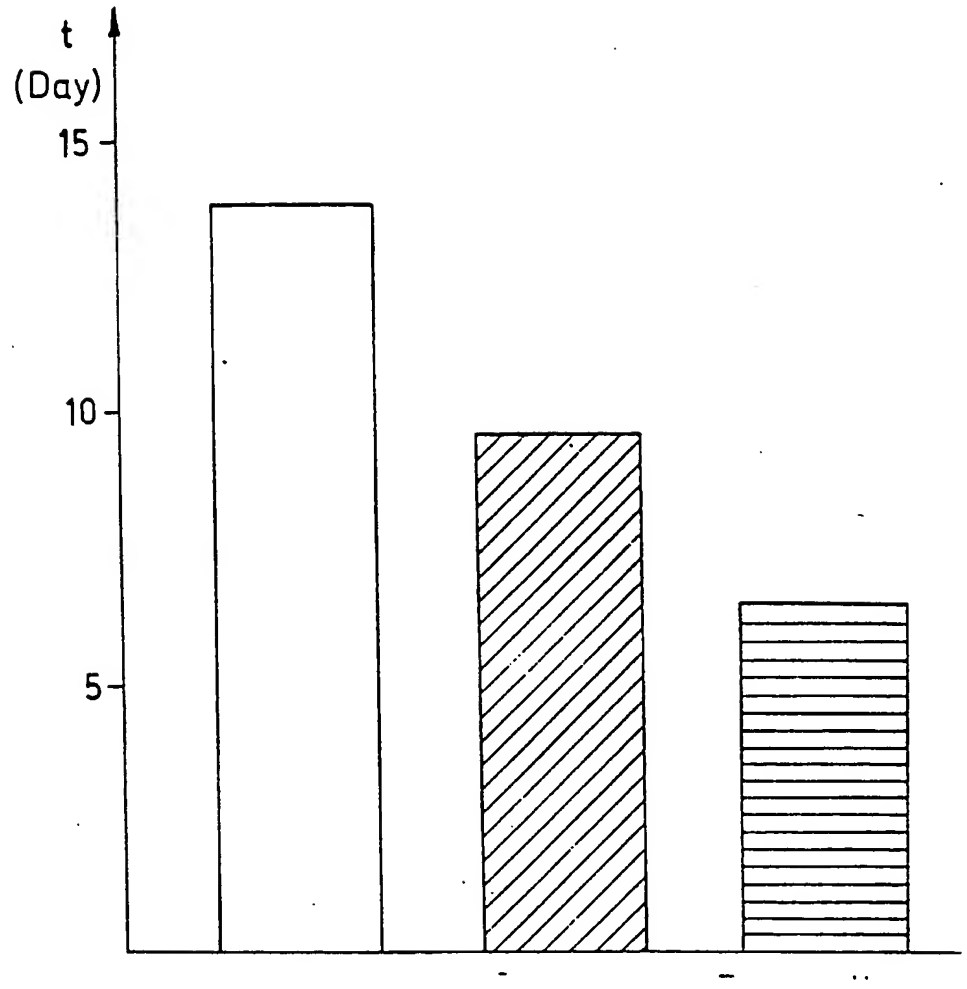

Fig.1

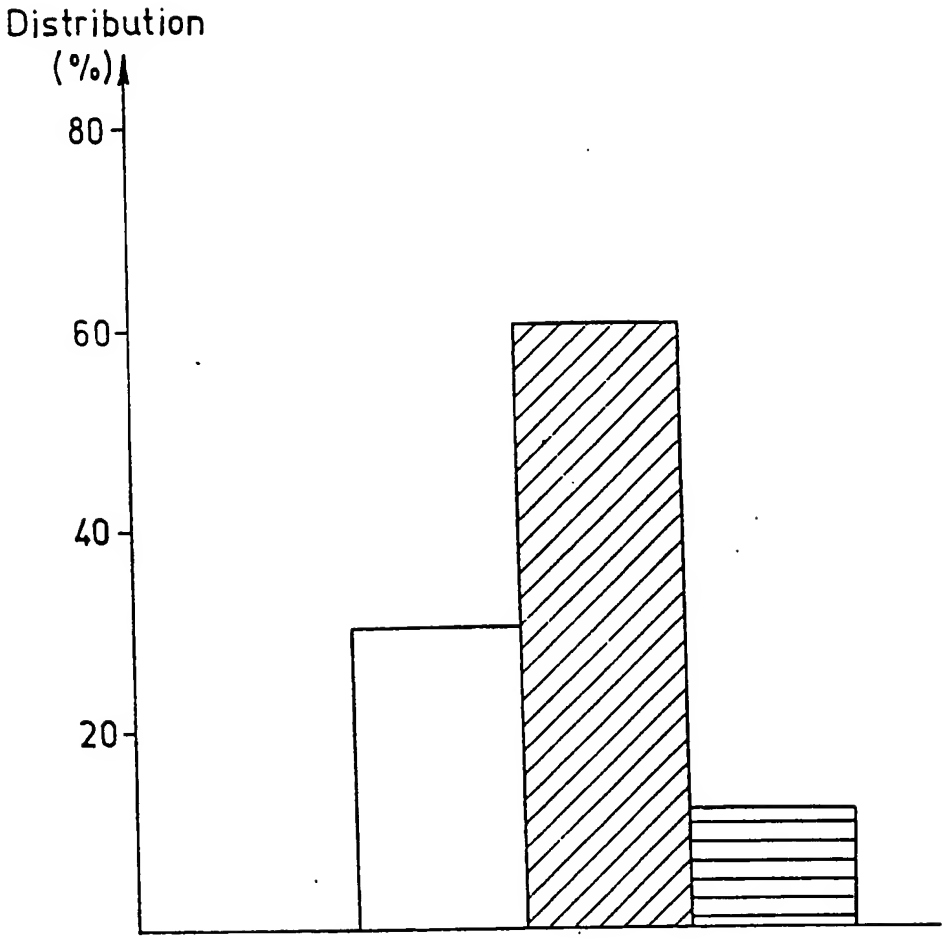

Fig. 2

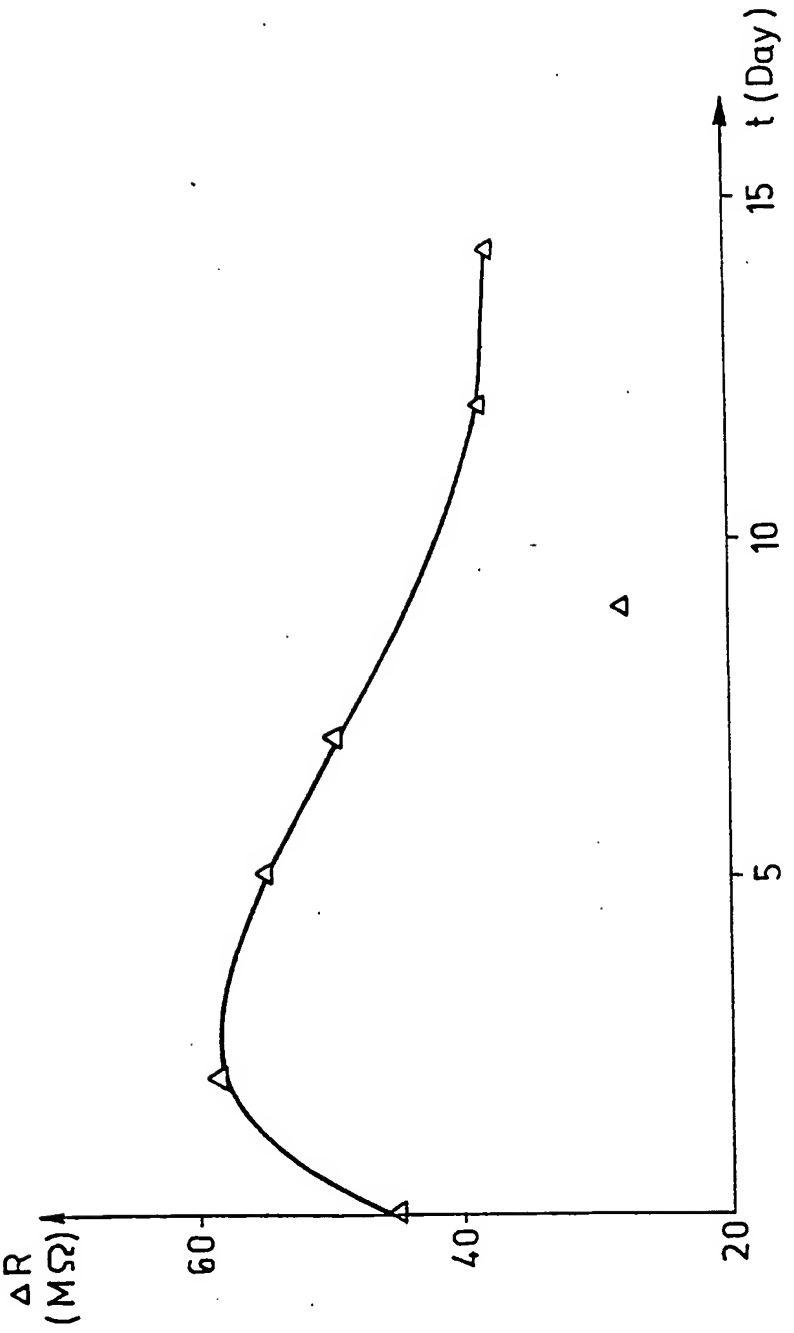

Fig.3

INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Patent Abstracts of Japan, unexamined applications Section C, Volume 16, no. 20, issued 1992, January 20, The Patent Office Japanese Government, page 17 C 902, the abstract no. 03-236 323 (KOBAYASHI KOSE CO LTD)..	1
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 93/00038

A. CLASSIFICATION OF SUBJECT MATTER

IPC[5]: A 61 K 31/70

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B. FIELDS SEARCHED

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IPC[5]: A 61 K 31/70

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS, WPIL; glycyrrhizin? glycyrrhizinic w acid) skin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 August 1993 (26.08.93)	07 September 1993 (07.09.93)

Name and mailing address of the ISA/ AT	Authorized officer
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/HU 93/00038

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